Body mass index and persistence of conventional DMARDs and TNF inhibitors in rheumatoid arthritis

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Abstract

Objective

Obese patients with rheumatoid arthritis (RA) may be more likely to discontinue therapy than non-obese patients, possibly signifying a more refractory phenotype. The purpose of this study was to examine the association between body mass index (BMI) and discontinuation rates for different RA treatments accounting for confounding factors.

Methods

Veterans Affairs administrative databases were used to define initial courses of methotrexate (MTX), hydroxychloroquine, sulfasalazine, prednisone, and self-injectable tumour necrosis factor inhibitors (TNFi). Discontinuation was defined as a lapse in drug refill >90 days. Using overweight BMI (25–30 kg/m²) as the referent group, multivariable Cox proportional hazards models were used to evaluate associations between BMI category and time to treatment discontinuation.

Results

There were 46,970 initial RA treatment courses identified from 2005-2014 among 23,669 Veterans with RA. In multivariable models, severe obesity (BMI >35 kg/m²), compared to overweight BMI, was not associated with treatment discontinuation with the exception of prednisone (HR 1.10 (1.04, 1.17) p<0.001). Patients with low (<20 kg/m²) and normal BMI (20–25 kg/m²) were more likely to discontinue MTX, TNFi, and HCQ compared to overweight patients. Other factors associated with earlier MTX and/or TNFi discontinuation included female sex, black race, greater comorbidity, depression, malignancy, congestive heart failure, current smoking, and more recent calendar year.

Conclusion

Obesity was not associated with therapy discontinuation among veterans with RA after accounting for confounding factors, suggesting that obesity is not a biological mediator of more refractory disease. Conversely, low BMI, comorbidity, and depression were identified as important predictors of drug discontinuation.

Key words

rheumatoid arthritis, obesity, anti-TNF drugs, DMARDs, drug persistence

Introduction

A growing literature reports associations between body mass index (BMI) and rheumatoid arthritis (RA) disease phenotype, including disease activity, progressive joint damage, disability, and treatment response. For example, several studies found that higher BMI was associated with a reduced risk of radiographic joint damage and extra-articular disease manifestations (1-3). Other studies, however, have demonstrated that patients with overweight or obese BMI tend to have higher levels of clinical disease activity and lower likelihood of achieving low disease activity compared to patients with normal or low BMI (4-7).

In addition to demonstrating lower likelihood of achieving remission among obese RA patients (4-8), a number of studies have also noted reduced clinical responses to tumour necrosis factor inhibitors (TNFi) in RA patients with high BMI (9-11), raising concern for a refractory RA treatment phenotype associated with obesity. Accordingly, greater therapy discontinuation might be expected among overweight and/or obese patients. To our knowledge, only one study has specifically evaluated the association between BMI and therapy discontinuation in RA (2). In this study, obese RA patients were >60% more likely to discontinue their initial TNFi [HR 1.64 (95% CI 1.02, 2.62)] and demonstrated the lowest rates of disease remission. With second TNFi exposures, the risk of discontinuation was even greater among obese patients, nearly three times greater than those with normal weight [HR 2.90 (95% CI 1.08, 8.45)].

It has been suggested that the chronic inflammation produced directly by excess adipose tissue could mitigate TNFi effectiveness and lead to more refractory disease in obese patients (9, 10, 12). However, given the lower rate of progressive radiographic damage reported in this group, alternative hypotheses also warrant consideration. Osteoarthritis, fibromyalgia, depression, and additional comorbid conditions and other factors that are more common in obesity may affect perceived RA disease activity and affect drug discontinuation.

In other words, it is possible that suboptimal therapeutic responses and earlier treatment discontinuations might be related to comorbid conditions that reduce perceived benefit and increase the risk of adverse events. This hypothesis is in contrast to that of a proposed direct biologic effect from adipose tissue. Previous studies that suggest a refractory disease phenotype have not adequately accounted for these potential confounders. The purpose of this study was to examine the association between BMI and disease-modifying anti-rheumatic drug (DMARD)/TNFi persistence, accounting for factors that may confound the relationship, including comorbidity.

Patients and methods

Study setting

The study design is a retrospective cohort study using real-world clinical data from 2005 to 2014 derived from Veterans Affairs (VA) administrative databases of US Veterans with RA. Analyses were performed among patients with at least one diagnosis code for RA in the 12 months prior to initiation of the course of RA therapy (International Classification of Diseases, 9th edition, 714.xx). Similar definitions of RA have demonstrated an 81–97% positive predictive value (13). Methods relevant to the identification of pharmacy drug courses and cohort derivation have been previously described (14). Briefly, pharmacy dispensing records were used to define the duration of unique initial drug courses of methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine, prednisone, and self-injectable TNFi (adalimumab, etanercept, golimumab, certolizumab). This analysis focused on self-injectable rather than intravenous TNFi preparations given greater difficulty in accurately characterising length of drug courses for intravenous formulations. We focused on TNFi rather than non-TNFi biologic agents as these are routinely considered first-line among currently available biologics and have the most frequent clinical use in RA. Likewise, the above listed DMARDs were analysed as these represent the majority of conventional DMARDs used to treat RA. Combination therapy was assessed by evaluating...
BMI and DMARD/TNF inhibitor persistence in RA / C. McCulley et al.

overlapping courses, and concomitant DMARDs were included as covari-
ables. Only the initial course of each drug for each patient was defined as a

drug course and a unique observation (15). Thus, a patient could contribute

initial VA-based courses for multi-
ple drugs but each patient would only

contribute one course for each of the

DMARDs under study.

Definition of treatment course length
For each dispensing episode, the

amount of drug dispensed and the ex-

pected duration of the treatment epi-

sode were determined. The expected
days of supply were determined based on
dosing instructions and the number of pills/units dispensed. A drug course was
defined as the duration of time in

which dispensing episodes did not have a

90-day gap from the end of the days’
supply of the last dispensing episode to

the start of the next dispensing episode

(14). Duration of treatment was cal-
culated as the time from the date of first
treatment until the date of the expected
end of the last dispensing episode for the
course. The primary outcome of interest was the course length (or per-
sistence) of the therapy, censoring for
death or end of follow-up. If patients
had multiple treatment courses of the

same medication, only the first treat-
ment course was included. Patients
could contribute multiple distinct treat-
ment courses for different medications.

Body mass index
Weight and height were extracted from

vital sign packages in the VA electronic
medical record. The closest value for

weight within 30 days of the start date
was used. When multiple different val-
ues for height were used, the modal
value was imputed. BMI [weight (kg)/
height(m)^2] was categorised per the

World Health Organization (WHO) as

underweight (<20 kg/m^2), normal
weight (20–25 kg/m^2), overweight
(25–30 kg/m^2), obese (30–35 kg/m^2),
and severely obese (≥35 kg/m^2) groups (16). The overweight group was found to
demonstrate the lowest likelihood of discontinuation across agents exami-
ned. This group was chosen as the ref-

erence category to enable comparisons

of other BMI categories to the most ex-
treme category and therefore minimise the likelihood of missing important as-
sociations. Courses missing BMI val-
ues within 30 days were excluded.

Potential confounders
Covariates of interest were derived from

administrative and laboratory da-
tabases from the medical record. These
included potential confounders hypo-
thesised to influence RA disease activity or treatment tolerability, including RA
disease duration, current smoking, calen-
age, sex, race (Black vs. White/Other),
anti-cyclic citrullinated peptide anti-
body (ACPA) status, and C-reactive
protein (CRP) concentration. The calen-
were divided as such and evaluated
separately due to the increased number of available biologics for RA treatment
in later years, which was thought to
temporally impact medication persis-
tence. Comorbidities were defined by

previously validated and published al-
gorithms using diagnosis codes for dia-
abetes, hypertension, congestive heart
failure (CHF), history of malignancy,
anxiety, and depression (17, 18). The

Rheumatic Disease Comorbidity Index
(RDCI) was also calculated for each
observation. The RDCI is validated
and was designed specifically to pre-
dict outcomes, including death, physi-

cal functioning and disability, medical
costs, social security disability, and
hospitalisations among patients with
rheumatic diseases (19).

Statistical analysis
Differences in patient characteristics

across BMI categories were tested using

analysis of variance (ANOVA) or
Kruskal-Wallis tests for non-parametric
data. To avoid dropping observations,
multiple imputation (5 imputations)
was performed to account for missing
values for CRP (77%), ACPA status
(27%), and disease duration (> or ≤
five years) (27%). Multivariable Cox
proportional hazards models were used to
evaluate associations between BMI
category and time to treatment discon-
tinuation before and after considering
potential confounding factors. Follow-

up time for each course was censored
at the first of 1) the end of the period
of observation, 2) the last vital signs
data recorded in the VA, or 3) death.
We performed sensitivity analyses af-

after clustering by patient and found no
impact on the results (not shown). The

proportional hazards assumption was

tested by visualising log-log plots and

Kaplan-Meier curves. We also per-
formed sensitivity analyses looking at
drug discontinuation and limiting the
follow-up period to 2 years. All analy-
ses were performed using Stata 14.0
software (StataCorp, LP, College Sta-
tion, TX) within the VA Informatics and
Computing Infrastructure (VINCI).

Results
There were 46,970 total unique ini-
tial DMARD or TNFi courses among
23,669 unique patients with RA be-
tween 2005–2014. Demographics of the
study population across BMI categories
are presented in Table I. There were a
number of significant differences in co-
variates across BMI categories. For ex-
ample, patients with normal BMI were

more likely to be ACPA-positive (70%) compared to the severely obese group

(57%). There were also a number of dif-
ferences in comorbid conditions across
BMI categories. Obese patients had

higher comorbidity scores and a greater
likelihood of having CHF compared to

normal weight (12% vs. 7%, respec-
tively). Patients with low BMI had the

highest frequency of a history of ma-
lignancy (17%), while severely obese

patients had the highest frequency of
anxiety (22%) and depression (44%).

In models adjusted only for age, sex,
race, and calendar year, patients with

severe obesity were more likely to dis-
continue MTX, TNFi, and prednisone

versus overweight patients (Table II).
However, the associations between se-
vere obesity and drug discontinuation

for MTX and TNFi in fully-adjusted

multivariable models were completely

attenuated (Table II, Fig. 1). Among
those receiving TNFi, there was a nu-
merical trend towards a greater risk of
drug discontinuation among those with

a disease duration >5 years [HR 1.14
(1.00, 1.29) p=0.056; n=4320]. This
trend was not present in those with early
Table I. Patient characteristics according to BMI category.

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Underweight &lt;20 kg/m²</th>
<th>Normal 20-25 kg/m²</th>
<th>Overweight 25-30 kg/m²</th>
<th>Obese 30-35 kg/m²</th>
<th>Severely Obese ≥35 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.</td>
<td>1,242</td>
<td>9,329</td>
<td>17,183</td>
<td>11,818</td>
<td>7,398</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>64.2 (12.6)</td>
<td>64.1 (12.5)</td>
<td>63.2 (11.2)</td>
<td>60.9 (10.4)</td>
<td>59.0 (9.5)</td>
</tr>
<tr>
<td>Male, n. (%)</td>
<td>1,064 (86%)</td>
<td>8,238 (88%)</td>
<td>15,448 (90%)</td>
<td>10,348 (88%)</td>
<td>6,118 (83%)</td>
</tr>
<tr>
<td>ACPA: anti-citrullinated peptide antibodies</td>
<td>96 (16%)</td>
<td>1,257 (13%)</td>
<td>2,235 (13%)</td>
<td>1,681 (14%)</td>
<td>1,113 (15%)</td>
</tr>
<tr>
<td>ACtIF: anti-citrullinated peptide antibodies</td>
<td>72%</td>
<td>70%</td>
<td>65%</td>
<td>60%</td>
<td>57%</td>
</tr>
<tr>
<td>RDCI 1 (0,2)</td>
<td>665 (54%)</td>
<td>5,462 (59%)</td>
<td>11,488 (67%)</td>
<td>8,760 (74%)</td>
<td>5,899 (80%)</td>
</tr>
<tr>
<td>CRP**</td>
<td>3.1 (3.9)</td>
<td>2.5 (3.5)</td>
<td>2.2 (3.4)</td>
<td>2.0 (3.4)</td>
<td>1.7 (3.2)</td>
</tr>
<tr>
<td>Disease &gt;5 yrs**</td>
<td>109 (84%)</td>
<td>1,078 (87%)</td>
<td>2,040 (84%)</td>
<td>1,446 (80%)</td>
<td>844 (63%)</td>
</tr>
<tr>
<td>BMI Category 20-25 kg/m²</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>1.03 (0.98, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.03 (0.98, 1.07)</td>
<td>1.01 (0.96, 1.07)</td>
<td>1.00 (0.96, 1.07)</td>
</tr>
<tr>
<td>≥35 kg/m²</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.02 (0.97, 1.07)</td>
</tr>
</tbody>
</table>

Values are represented as mean (SD) or median (IQR) for skewed data unless otherwise noted. All p-values based on ANOVA and Kruskal-Wallis tests of significance at p<0.001.

*Calendar date of the start of the course observation; **Includes imputed values. SD: standard deviation; RDCI: Rheumatic Disease Comorbidity Index; ACPA: anti-citrullinated peptide antibodies; CHF: congestive heart failure; HTN: hypertension.

Table II. Associations between BMI category and earlier drug discontinuation.

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>TNFi</th>
<th>Prednisone</th>
<th>HCQ</th>
<th>SSZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued: 14,770</td>
<td>Discontinued: 8,313</td>
<td>Discontinued: 11,349</td>
<td>Discontinue: 7,287</td>
<td>Discontinued: 4,299</td>
</tr>
<tr>
<td>Partially-adjusted</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>BMI Category &lt;20 kg/m²</td>
<td>1.14 (1.02, 1.27)**</td>
<td>1.13 (0.96, 1.33)</td>
<td>0.96 (0.85, 1.07)</td>
<td>1.12 (0.96, 1.30)</td>
</tr>
<tr>
<td>20-25 kg/m²</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.13 (1.06, 1.21)**</td>
<td>0.92 (0.87, 0.97)**</td>
<td>1.09 (1.02, 1.16)**</td>
</tr>
<tr>
<td>25–30 kg/m²</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>≥35 kg/m²</td>
<td>1.06 (1.00, 1.11)*</td>
<td>1.07 (1.00, 1.14)*</td>
<td>1.10 (1.04, 1.17)**</td>
<td>0.95 (0.89, 1.02)</td>
</tr>
</tbody>
</table>

Fully-adjusted | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| BMI Category <20 kg/m² | 1.13 (1.01, 1.26)** | 1.18 (1.00, 1.39) | 0.95 (0.84, 1.06) | 1.10 (0.94, 1.29) | 0.98 (0.79, 1.22) |
| 20-25 kg/m² | 1.04 (0.99, 1.09)* | 1.14 (1.07, 1.22)** | 0.93 (0.88, 0.98)* | 1.08 (1.01, 1.16)** | 1.06 (0.97, 1.16) |
| 25–30 kg/m² | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| ≥35 kg/m² | 0.99 (0.94, 1.03) | 1.02 (0.97, 1.09) | 1.03 (0.98, 1.08) | 0.97 (0.91, 1.03) | 0.97 (0.89, 1.05) |

* p<0.05; ** p<0.01; *** p<0.001

†Adjusted for calendar date, age, sex, black race. For TNFi: also adjusted for drug name and initial vs. subsequent biologic course.

‡Also adjusted for: Concurrent medication use (HCQ, SSZ, MTX, prednisone, TNFi), RDCI, ACPA-positive, disease duration >5 years, diabetes, HTN, CHF, anxiety, depression, current smoking. For TNFi: also adjusted for first biologic use and therapy.

BMI: body mass index; HR: hazard ratio; TNFi: tumour necrosis factor inhibitor; RDCI: Rheumatic Disease Comorbidity Index; ACPA: anti-citrullinated peptide antibody; CHF: congestive heart failure.

disease [HR 0.95 (0.87, 1.04) p=0.29; n=2747]. In sensitivity analyses limiting the analysis to 2 years of follow-up, severe obesity was not associated with drug discontinuation in adjusted models except for among those receiving prednisone [HR 1.23 (1.10, 1.37) p<0.001]. In contrast to MTX and TNFi, the association of severe obesity with discontinuation of prednisone remained significant [HR 1.11 (1.04, 1.18) p=0.001] in fully adjusted models. Obesity was less associated with the discontinuation of HCQ or sulfasalazine in either univariate or multivariate analyses. Patients in low and normal BMI categories generally were more likely to discontinue MTX, HCQ, and TNFi, compared to overweight patients, and these associations persisted in fully-adjusted multivariable models (Table II). In contrast, patients with normal BMI were less likely than overweight patients to discontinue prednisone, even in fully-adjusted models. Table III shows other factors associated with DMARD discontinuation for MTX, TNFi, prednisone, HCQ, and sulfasalazine. Factors associated with earlier MTX discontinuation included female sex, black race, greater comorbidity, depression, anxiety, CHF, active smoking, ACPA-negativity, and more
recent calendar year (Table III). Among TNFi users, female sex, older age, greater comorbidity, depression, malignancy, smoking, concurrent prednisone use, and recent calendar year were independently associated with a greater likelihood of discontinuation. Concurrent MTX use was associated with a lower likelihood of TNFi discontinuation [HR 0.89 (0.85, 0.93) \(p<0.001\)]. Initial TNFi users were less likely to discontinue therapy than those starting a subsequent TNFi.

Among prednisone users, greater use of other therapies, female sex, more recent calendar year, depression, anxiety, and smoking were each associated with a greater likelihood of discontinuation. Patients who were ACPA-positive were less likely to discontinue prednisone.

**Discussion**

This large, real-world, national study demonstrated that obesity was not associated with discontinuation of conventional DMARDs and/or TNFi’s when considering differences in other factors including comorbid conditions. While there was modestly greater discontinuation among the severely obese in crude analyses, there was no association between obesity and DMARD/TNFi discontinuation in adjusted models. These data refute the hypothesis that obesity and excess adiposity directly interfere with the biological effect of commonly prescribed RA therapies. Given the growing number of treatments available for rheumatoid arthritis (20), consideration of comorbidities is increasingly important to guide clinical decision making and treatment choice.

A decreased response rate and increased discontinuation rates of DMARD/TNFi among obese RA patients have been demonstrated in several smaller studies (2, 9, 10, 21) and among patients with other types of inflammatory arthritis (22). The current study confirms greater drug discontinuation among the severely obese, but the lack of association after multivariable adjustment suggests that this phenomenon is not likely to be a causal effect of excess weight. Rather, the slightly higher discontinuation rates among severely obese patients in this study were not independent of confounding factors. We hypothesise that comorbid conditions and other factors among obese individuals, and not refractory RA disease activity, drive more frequent DMARD/TNFi changes. More frequent medication changes in obese individuals may be appropriate in certain contexts (i.e. when a co-morbidity is a contraindication for a specific therapy), but might also occur for other reasons (i.e. false elevation in estimation of disease activity which may reflect other disease processes such as fibromyalgia, depression or osteoarthritis). Heimans and colleagues demonstrated this trend in the BeSt (Treatment Strategies for Rheumatoid Arthritis) trial, in which they found that patients with high BMI had higher DAS scores that were driven primarily by higher pain and joint tenderness scores, resulting in significantly more treatment steps over 8 years compared to patients with low/normal BMI (12). Swollen joint counts, however, are not associated with BMI and do not apparently perform worse in RA patients with greater BMI (23).

In contrast to the lack of association between obesity and drug discontinuation observed in this study, low BMI was consistently associated with greater DMARD and TNFi therapy discontinuation after adjustment for confounders. This finding may align with evidence that RA patients with low BMI tend to have more erosive and severe disease as demonstrated on MRI and radiographic imaging (24, 25), and supports the hypothesis that patients with a low BMI have a refractory phenotype of disease.

In support of this hypothesis, prednisone is less likely to be discontinued among patients with a normal BMI compared to those that were overweight or obese. However, it is possible that unmeasured confounding, discontinuation of therapy due to worsening health status, and more frequent side-effects in this group may play a role in explaining these associations.

Prednisone was generally discontinued earlier among severely obese patients, in contrast to other DMARDs. Complications of prednisone use may be more frequent in the severely obese (or physicians and patients may be more fearful or have a lower tolerance of such complications). The authors are not aware of studies that examine adverse glucocorticoid effects in obese patients compared to normal or underweight patients. The adverse effects of long-term glucocorticoid use, however, including morphologic changes in adipose distribution, hyperglycemia, infection risk, and cardiovascular risk, among others, might be hypothesised to be of greatest relevance in this group (26).
Table III. Association between covariates of interest and earlier drug discontinuation.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Methotrexate</th>
<th>TNFi</th>
<th>Prednisone</th>
<th>HCQ</th>
<th>SSZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=15,082</td>
<td>n=8,412</td>
<td>n=11,627</td>
<td>n=7,490</td>
<td>n=4,359</td>
</tr>
<tr>
<td>Discontinued: 14,770</td>
<td>Discontinued: 8,313</td>
<td>Discontinued: 11,349</td>
<td>Discontinued: 7,287</td>
<td>Discontinued: 4,299</td>
<td></td>
</tr>
<tr>
<td>Age &lt;60 yrs</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>60–70 yrs</td>
<td>0.82 (0.79, 0.86)***</td>
<td>0.89 (0.84, 0.94)**</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.92 (0.86, 0.97)*</td>
<td>0.90 (0.83, 0.97)**</td>
</tr>
<tr>
<td>70–80 yrs</td>
<td>0.88 (0.83, 0.93)*</td>
<td>0.92 (0.85, 0.99)</td>
<td>0.98 (0.93, 1.04)</td>
<td>0.94 (0.87, 1.02)</td>
<td>0.96 (0.86, 1.06)</td>
</tr>
<tr>
<td>&gt;80 yrs</td>
<td>0.94 (0.87, 1.02)</td>
<td>1.14 (0.99, 1.32)**</td>
<td>0.88 (0.81, 0.96)*</td>
<td>1.12 (1.05, 1.34)**</td>
<td>0.97 (0.82, 1.14)</td>
</tr>
<tr>
<td>Male</td>
<td>0.90 (0.85, 0.95)*****</td>
<td>0.80 (0.75, 0.86)*****</td>
<td>0.86 (0.81, 0.91)*****</td>
<td>0.93 (0.86, 1.00)</td>
<td>0.86 (0.78, 0.96)*****</td>
</tr>
<tr>
<td>Concurrent TNFi use</td>
<td>1.13 (1.07, 1.19)*****</td>
<td>1.08 (1.00, 1.16)</td>
<td>1.05 (0.99, 1.11)</td>
<td>1.31 (1.22, 1.41)*****</td>
<td>1.17 (1.07, 1.28)*****</td>
</tr>
<tr>
<td>ACPA-positive</td>
<td>1.09 (1.04, 1.14)*****</td>
<td>1.14 (1.09, 1.21)*****</td>
<td>1.08 (1.03, 1.13)*****</td>
<td>1.14 (1.08, 1.21)*****</td>
<td>1.13 (1.05, 1.22)*****</td>
</tr>
<tr>
<td>CHF</td>
<td>1.11 (1.06, 1.17)*****</td>
<td>1.06 (1.00, 1.13)</td>
<td>1.16 (1.09, 1.22)*****</td>
<td>1.01 (0.95, 1.09)</td>
<td>0.98 (0.90, 1.07)*****</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.09 (1.02, 1.17)**</td>
<td>1.06 (0.96, 1.17)</td>
<td>1.06 (0.99, 1.14)</td>
<td>0.96 (0.87, 1.06)</td>
<td>1.01 (0.90, 1.13)**</td>
</tr>
<tr>
<td>Comorbidities Score (RDCI)</td>
<td>1.05 (1.00, 1.11)</td>
<td>1.11 (1.03, 1.20)*</td>
<td>1.00 (0.94, 1.06)</td>
<td>1.05 (0.95, 1.10)</td>
<td>1.01 (0.92, 1.11)*</td>
</tr>
<tr>
<td>2005–2009 vs. 2009–2014</td>
<td>1.10 (1.05, 1.15)*****</td>
<td>1.10 (1.04, 1.20)*****</td>
<td>1.29 (1.21, 1.36)*****</td>
<td>1.09 (1.03, 1.16)*****</td>
<td>0.98 (0.90, 1.06)*****</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.07 (1.00, 1.13)*</td>
<td>1.11 (1.04, 1.20)*****</td>
<td>1.14 (1.07, 1.22)*****</td>
<td>1.07 (0.99, 1.15)</td>
<td>1.02 (0.92, 1.12)**</td>
</tr>
<tr>
<td>ACPA-positive</td>
<td>0.87 (0.83, 0.91)*****</td>
<td>0.94 (0.87, 1.01)</td>
<td>0.90 (0.86, 0.95)*****</td>
<td>0.95 (0.89, 1.02)</td>
<td>0.97 (0.88, 1.06)*****</td>
</tr>
<tr>
<td>Concurrent Prednisone</td>
<td>0.97 (0.93, 1.01)</td>
<td>1.13 (1.07, 1.16)*****</td>
<td>N/A</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.07 (1.00, 1.15)*</td>
</tr>
<tr>
<td>Concurrent MTX use</td>
<td>N/A</td>
<td>0.89 (0.85, 0.93)*****</td>
<td>0.97 (0.93, 1.00)</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.94 (0.88, 1.01)*****</td>
</tr>
<tr>
<td>Concurrent TNFi use</td>
<td>N/A</td>
<td>1.14 (1.07, 1.21)*****</td>
<td>1.10 (0.99, 1.20)</td>
<td>1.09 (1.00, 1.21)*</td>
<td>1.07 (0.95, 1.20)*****</td>
</tr>
<tr>
<td>Concurrent SSZ use</td>
<td>1.05 (0.96, 1.14)</td>
<td>0.96 (0.88, 1.05)</td>
<td>1.13 (1.03, 1.25)*</td>
<td>1.11 (1.02, 1.22)*</td>
<td>N/A</td>
</tr>
<tr>
<td>Initial Biologic</td>
<td>N/A</td>
<td>0.87 (0.82, 0.91)*****</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HR (95% CI) HR (95% CI) HR (95% CI) HR (95% CI) HR (95% CI)

*p<0.05; **p<0.01; ***p<0.001.

Additional variables were included in the models and are not shown (BMI category) or non-significant (CRP, disease duration >5 years, concurrent HCQ, diabetes, hypertension).

CHF: congestive heart failure; RDCI: Rheumatic Disease Comorbidity Index; ACPA: anti-cyclic citrullinated peptide antibody; MTX: methotrexate; TNFi: tumour necrosis factor inhibitor; SSZ: sulfasalazine; CRP: C-reactive protein; HCQ: hydroxychloroquine.

A limitation of this retrospective analysis of health records data is that it does not provide the opportunity to evaluate individual patients on a more granular level. This national VA database does not include disease activity scores, so this potentially important clinical information was unavailable in these analyses. While a strength is the presence of laboratory data in this administrative database, ACPA status was missing for many patients and thus necessitated imputing values to allow incorporation of ACPA into multivariable models. Drug discontinuation was determined using pharmacy data, which may not accurately reflect actual use of therapies in every case. For example, prednisone use is often not utilised exactly as directed. Additionally, it is not possible to determine whether individual discontinuations occurred because of lack of efficacy, adverse reactions or intolerance, patient preference, poor adherence, socioeconomic factors, or other reasons. However, medication persistence is a well-established proxy for efficacy. The methodology does not capture temporary medication discontinuations either. Additionally, data are derived from the US Veteran population, with over-representation of Caucasian and male patients. However, no interactions between sex or racial groups were identified, suggesting that these findings may be generalisable beyond the VA health system. Additionally, it can be challenging to identify true synovitis in obese patients, and it is possible that an equivocal physical exam may overestimate disease activity and subsequently affect medication persistence. The reasons for discontinuation in the different BMI categories cannot be assessed here, and this is an important limitation. Furthermore, our analysis only looks at BMI at a single point in time, and it is known that weight changes over the lifespan and that these changes may be informative. Finally, dual care from the VA and the public sector could result in prescriptions that are not captured in VA databases, although recent work suggests that this is uncommon in part related to generally better health benefits through the VA compared to civilian benefits (27).

The study has several notable strengths. First, the cohort was large, including over 45,000 unique initial DMARD or TNFi courses in the analysis. The study is an advancement over prior studies in its use of robust clinical data from the electronic medical record as well as well-defined drug courses using pharmacy records, allowing for a comprehensive and well-powered analysis. Our findings also capture national data as opposed to one region of the country. This study is among the first to comprehensively analyse the association between BMI and drug discontinuation while accounting for potentially significant confounding factors in a nationwide sample.

In conclusion, this study did not demonstrate an association between BMI and DMARD/TNF inhibitor discontinuation rates after adjusting for important covariates. While these data do not support the hypothesis that obesity contributes to poor treatment efficacy or tolerability, we cannot rule out biologic differences in response to therapy. However, other factors including co-morbidities were identified as important predictors of drug discontinuation.
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References